The Correlation between galectin-3, creatinine and uric acid on stage V chronic renal failure

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THE CORRELATION BETWEEN GALECTIN-3,CREATININE AND URIC ACID ON STAGE V CHRONIC RENAL FAILURE

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ABSTRACT

Chronic Renal Failure (CRF) is structural damage and function of the kidneys that cannotexcrete toxins and waste products from the blood, characterized by the presence of protein in the urine and decreased glomerulus filtration rate. This study aimed to determine the correlation between Galectin-3 and markers of kidney function which are creatinine and uric acid. This study was being concluded on 33 CRF patients whowere doing hemodialysis therapy. This study was conducted in the Dr. Kariadi Semarang Hospital and GAKI Laboratory of Diponegoro Medical Faculty from April to June 2018. The research method was analytical descriptive with cross-sectional approach. Galectin-3 was analyzed using ELISA method with an automatic analyzer, creatinine and uric acid using the colorimetric method with an automaticspectrophotometer. Statistical analysis used Shaphiro-Wilk normality test and Spearman correlation test. There is a weak positive correlation test of galectin-3 with creatinine (r = 0.381; p = 0.029) and galectin-3 with uric acid (r = 0.374; p = 0.048) in CRF – HD.It is concludedgalectin-3 can be used as a marker of kidney function.

Key words: Galectin-3, creatinine, uric acid, chronic renal failure, hemodialysis

INTRODUCTION

Chronic kidney failure is a world health problem with an increased incidence, prevalence, and level of morbidity. Hypertension, diabetes, smoking, the use of analgesic drugs, NSAIDs, and the use of energy drinks affect the occurrence of Chronic Renal Failure (CRF). Chronic renal failure generally develops to the terminal stage or the final stage requiring renal function replacement therapy, known as dialysis.[1,2] Chronic renal failure lasts for at least three months and can cause persistent kidney disease.[3,4] Long-term disease, such as hypertension and diabetes, slowly damage the kidneys and reduce kidney function over time. End-Stage Renal Disease (ESRD) requires renal replacement therapy namely Hemodialysis (HD), Continuous Ambulatory Peritoneal dialysis (CAPD) or a kidney transplant to maintain the patients survival.[5]

Galectin-3 is a protein molecule, belonging to the galactoside binding family of lectins that bind β-galactoside to glycoprotein and glycolipid cells also known as IgE binding proteins, laminin binding proteins, and Mac-2 antigens. Galectin-3 is involved in various biological processes such as inter-cell adhesion, proliferation, malignant transformation, and metastasis. Excessive levels of galectin-3 in the body play a role in promoting the inflammatory and fibrotic response that causes progressive heart failure, liver cirrhosis, and renal failure. Research by Li *et al*. and Drechsler *et al*. stated that galectin-3 concentrations increased with progressive kidney damage.[6,7]

Creatinine is a residual product of reshaping creatine phosphate that mostly occurs in the muscle (98%) and the rest in the heart, liver, brain, kidneys and body fluids.[8] Creatinine levels are influenced by muscle mass, diet, physical activity, sex and age, but it is relatively stable over time. Small muscle mass cause little creatinine production.[9] Creatinine is excreted through the urine, so the kidneys are responsible for creatinine levels in the blood.[3,4,9] Permanent abnormal high creatinine levels indicate damage or failure of chronic kidney function and can sometimes be detected before the presence of symptoms.[10,11]

Uric acid is the final product of adenine and guanine catabolism derived from the breakdown of purine nucleotides. Uric acid is the final product of purine metabolism which consists of carbon, nitrogen, oxygen, and hydrogen components with the molecular formula of C5H4N4O3. Johnson *et al.*

stated that the kidneys are responsible for excretion of two-thirds of uric acid levels every day and the other third is excreted through the gastrointestinal tract.[11]

Chronic renal failure is known to involve an inflammatory process and fibrosis as the pathogenesis of damage to the glomerulus and renal tubules until the kidneys lose their function. Detection of renal dysfunction by urinalysis are albuminuria, hematuria and the presence of urine sediment abnormalities, and need confirmation by other examinations such as serum creatinine and uric acid parameters.[10-12] It is known that an increase in galectin-3 levels influences the development of CRF associated with a decrease in Glomerular Filtration Rate (GFR) with abnormally high creatinine levels as a sign of glomerular filtration function and an increase in uric acid levels or hyperuricemia as a marker of tubular reabsorption and secretion function which indicates damage or failure of kidney function.[12] creased in patients with decreased GFR, but there have not been many studies that state galectin-3 levels in various stages of CRF.[8] This study wants to prove galactin-3 as a potential novel biomarker in patients with CRF stage V.

METHODS

This study was a descriptive analytic study with a cross-sectional approach to analyzing galectin-3 levels, creatinine levels and uric acid levels as outputs in CRF patients with hemodialysis. Data were coded, entered, cleaned and edited on software programs. Univariate analysis was performed on each variable to determine the characteristics of the sample. Bivariate analysis was conducted to find the relationship between galectin-3 levels and creatinine levels, and galectin-3 levels with uric acid levels in CRF patients with hemodialysis. The inclusion criteria were patients with CRF who received hemodialysis therapy, and willing to sign an informed consent, and had examination of creatinine, uric acid, and galectin-3. Exclusion criteria were as follows: age <18 years, psychiatric illness, and severe comorbidity affecting outcome and prognosis, including cancer, acute hepatocellular insufficiency, acute infectious disease, and exacerbation of chronic diseases. Lysed samples were also excluded. Galectin-3 was analyzed with ELISA method. Creatinine and uric acid using the colorimetric method.

Data normality test was done from each variable using Shapiro-Wilk. The results of the normality test for each data showed that uric acid levels were normally distributed while galectin-3 and creatinine levels were distributed abnormally even after data transformation, so the Spearman correlation test was carried out. Relationships were considered significant if $p \leq 0.05$. The degree of relationship showed a very weak relationship if r=0-0.199, weak relationship if r=0.2-0.399, moderate relationship if r=0.4-0.599, strong relationship if r=0.6-0.799 and the relationship was very strong if r=0.8-1.00

This study has obtained ethical clearance No.172 / EC / FK-RSDK / IV / 2018 dated 17 April 2018 from the Health Research Ethics Committee of the FK UNDIP/Dr. Kariadi Hospital. All research subjects/families were asked for their approval by signing written informed consent. The patient's identity was kept confidential, and all costs related to the research were the responsibility of the researcher. All prospective research subjects were given a full explanation of the objectives, benefits and research procedures. Research subjects have the right to refuse to be included in the study.

RESULTS AND DISCUSSION

This study was conducted on CRF patients who did hemodialysis at the Dr. Kariadi Hospital Semarang. Blood samples were examined in the Semarang IDD laboratory in April 2018 - June 2018. A total of 35 samples were collected, two lysis samples were excluded from this study and 33 samples fulfilled the inclusion and exclusion criteria who were willing to sign an informed consent during this period. The study involved 33 patients with the youngest males aged 20 years and the oldest was 62 years. Based on the classification of CRF according to the degree of disease, all patients involved in this study were in the 5th-grade category with a GFR of less than 15 mL/minute. Glomerular Filtration Rate (GFR) used: Chronic Epidemiology Collaboration Equation (CKD-EPI). This study also assessed the condition of hypertension, diabetes mellitus, kidney trauma and consumption of energy drinks/herbs which are considered as risk factors for CRF. It can be seen in Table 1. Patients who had hypertension were 20 cases, diabetes mellitus were three cases, kidney stones were 8 cases and a history of energy drinks or herbal medicine consumption were two cases from all study samples.

The characteristic data of the study sample are shown in Table 2. Data with normal distribution were BMI parameters, systolic blood pressure, while the data with abnormal distribution were parameters of age, weight, height, diastolic blood pressure, galectin-3, creatinine, and uric acid levels. Statistical

Table 1. Descriptive data on risk factors for chronic renal failure

Risk factor	Total	Percentage (%)
Hypertension	20	60
Diabetes	3	8
Kidney stones	8	25
History of energy drinks/ herbal medicine consumption	2	6

tests for data normality use the Shapiro-Wilk normality test. Data were normally distributed if $p > 0.05$.

Data on galectin-3 levels and serum creatinine were abnormally distributed based on data transformation. Spearman correlation test was used to test the relationship in two variables. The relationship test results between galectin-3 levels and creatinine levels obtained were $r = 0.381$ with $p = 0.029$, meaning there was a weak positive relationship. A scatter chart plots the relationship of serum galectin-3 levels with serum creatinine levels in CRF patients with hemodialysis can be seen in Figure 1.

Data on galectin-3 levels and serum uric acid levels were abnormally distributed based on data transformation. Spearman correlation test was used to test the relationship in two variables. The test results of the relationship between galectin-3 levels and serum uric acid levels were obtained $r = 0.347$ with $p = 0.048$, meaning there was a weak positive relationship. A scatter plot graph of the relationship of galectin-3 levels with serum uric acid levels in patients with CRF with hemodialysis can be seen in Figure 2.

This study involved 33 CRF patients with hemodialysis who fulfilled the inclusion and

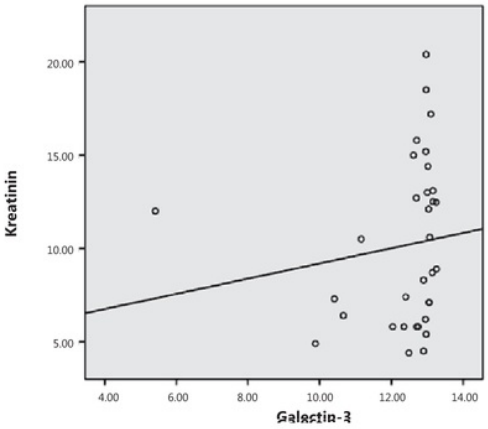

Figure 1. Scatter chart plots the relationship of serum galectin-3 levels with serum creatinine levels in CRF patients with hemodialysis

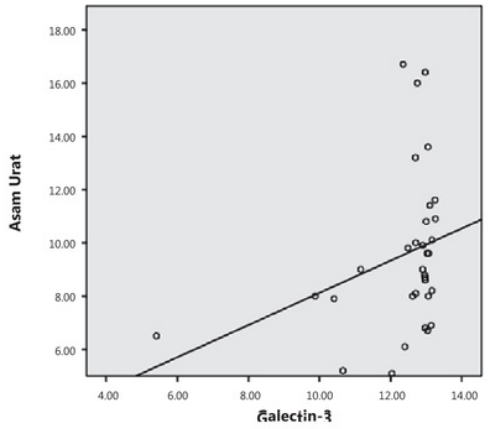

Figure 2. Scatter chart plot of the relationship between galectin-3 levels and serum uric acid levels in patients with CRF with hemodialysis

Table 2. Characteristics of research sample data

Variable	Mean ± SD	Median (min – max)	Normality	
			p	Transf.
Age (years)	46.33 ± 10.09	45 (20 – 62)	0.238	0.246
Weight (kg)	63.73 ± 5.17	63 (52 – 73)	0.033	0.034
Height (cm)	167.65 ± 4.37	169 (150 – 175)	0.000	0.000
BMI	22.56 ± 1.51	22.43 (18.44 – 25.00)	0.576	
Systolic (mmHg)	150.30 ± 19.92	150 (110 – 180)	0.084	
Diastolic (mmHg)	116.36 ± 157.02	90 (70 – 990)	0.000	0.000
Galectin-3 (ng/dL)	12.43 ± 1.55	12.95 (5.41 – 13.97)	0.000	0.000
Creatinine (mg/dL)	10.16 ± 4.43	8.9 (4.4 – 20.4)	0.035	0.123
Uric acid (mg/dL)	9.55 ± 2.96	9 (5.1 – 16.7)	0.014	0.544*

Note: * normal data distribution
BMI: Body Mass Index

exclusion criteria, all of them were male. The youngest age was 20 years, and the oldest was 62 years. Research by Dharma stated that the incidence of CRF was increasingly prevalent in young adults.[13] This finding is due to increasing unhealthy lifestyles such as consuming fast food, stress, smoking, lack of body activity, energy drinks, and rare consuming of water.[13,14] These poor habits are a risk factor for kidney damage.

According to the data from the Indonesian Renal Registry (IRR) in 2012, the risk factors for CRF that occur mostly in young adults were Diabetes Mellitus (DM), hypertension, smoking habits and consumption of supplemental drinks.[15] Risk factors that influence the high incidence of CRF were unmodified factors such as age, sex, race, genetics, and modified factors such as hypertension, diabetes mellitus, kidney stones, anddiet can influence the incidence of CRF. Hypertension was the highest risk factor in the subject of this study. It was found that 60% of patients were with hypertension. There were 25% nephrolithiasis patients and 9% of DM patients. About 6% of people had a history of consuming energy supplement and herbal drinks for a long time.[15,16]

Uncontrolled hypertension can worsen disease progression by causing arteriolar nephrosclerosis due to the hyperfiltration process.[16-17] Hyperfiltration injury is a general course of glomerular damage. It does not depend on the underlying cause of kidney damage. With the loss of nephrons, the remaining nephrons experience structural and functional hypertrophy characterized by increased glomerular blood flow. The driving force for glomerular filtration is the increase in living nephrons. Although the mechanism of hyperfiltration can temporarily maintain kidney function, it will subsequently lead to progressive damage to living glomeruli, due to the direct effect of increased hydrostatic pressure on the integrity of capillary walls and/or the effects of increased protein across the capillary wall. Over time, with an increased sclerosing nephrons population, surviving nephrons will experience an increased burden of excretion, which will cause a vicious cycle of hyperfiltration and increased glomerular blood flow, associated with intravascular volume overload and/or excessive renin production associated with glomerular disease.[18]

Nephrolithiasis is the crystallization of minerals and matrixes such as pus, blood, tissue, and tumors. The increase in solution concentration is a result of low intake and also an increase in organic matter due to infection of the urinary tract or static urine thus making a place for stone formation. Kidney stones cause some nephrons (including glomeruli and tubules) to be damaged. Intact nephrons undergo hypertrophy, furthermore because the number of damaged nephrons increases, oliguria, and retention of residual products arise. The symptoms in the patient become more explisit, and there are typical symptoms of kidney failure if approximately kidney function has disappeared 80% - 90%. The renal function becomes low at this level, and creatinine clearance values drop to 15 mL/ minute or lower.[17]

The condition of hyperglycemia in patients with uncontrolled DM will force the glomerulus and tubules to work harder infiltration, secretions, and reabsorption which will slowly damage the kidney nephron. Damage to the kidney nephron will be more extensive and continuous in uncontrolled DM conditions until kidney damage occurs due to diabetes is known as diabetic nephropathy. This condition generally continues towards CRF which ends with hemodialysis as a therapy for kidney replacement.[13]

According to Dharma, supplement drinks are related to the wrong eating and drinking habits.[13] People tend to be lazy to consume nutritious food and then switch to supplements as a substitute for vitamin intake. Supplements contain synthetic vitamins resulting from chemical products that are not free from carcinogenic substances. Excessive consumption of supplemental beverages can aggravate kidney work. The supplements are containing various substances, including taurine and caffeine. Taurine is a detoxifying amino acid that gives an effect like glycine in neutralizing all types of toxins, but excess consumption of taurine in supplements in amounts that exceed the threshold of 50-100 mg makes the kidneys work harder. According to Hidayati, caffeine can narrow the arteries to the kidneys so that the blood leading to the kidneys decreases.[14] As a result, the kidneys will lack food intake and oxygen. The state of kidney cells lacking oxygen and food will cause kidney cells to experience ischemia and spur the emergence of an inflammatory reaction that can end with a decrease in the ability of kidney cells to filter blood.[14] The supplemental drink also contains several dangerous chemicals such as preservatives, food coloring, flavorings, and artificial sweeteners. Research conducted by Nugroho concluded that the more frequent consumption of supplements could lead to faster kidney damage.[19]

Galectin-3 levels in the study subjects had a mean value of 12.43 ± 1.55 with the lowest levels of 5.41 ng/mL and the highest of 13.97 ng/mL. Galectin-3 serum levels in this study were within normal limits. Galectin-3 is a profibrotic mediator that is elevated in CRF with progressive fibrosis. Normal galectin-3 serum levels can occur because CRF patients with hemodialysis have achieved stable and permanent fibrosis in the kidneys so that galectin-3 secretion as a profibrotic marker return to normal or decreased. The fibrogenesis of the kidneys that runs for more than four months has stabilized which means that the inflammatory and fibrosis processes in the kidneys have been reduced.[20,21] The development of CRF is characterized by the development of glomerular and tubular fibrosis where galectin-3 is a profibrotic mediator in the kidneys which increases in progressive fibrosis.[22]

Creatinine levels in this study had a mean value of 8.9 mg/dL with the lowest level of 4.4 mg/dL and the highest level of 20.4 mg/dL. The creatinine in this study was used as a parameter for evaluating glomerular function,wherein normal conditions almost all creatinine would be filtrated in the glomerulus and then excreted through urine. Increased serum creatinine levels indicate glomerular filtration failure, where creatinine is used to assess GFR to determine the need for dialysis as a therapy for renal replacement in CRF patients.[23]

Uric acid levels in this study had a mean of 9.0 mg/dL with the lowest levels of 5.1 mg/dL and the highest levels of 16.7 mg/dL. Uric acid in this study was used as a parameter for the assessment of tubular function where most uric acid would be absorbed, partly secreted by the tubules and discharged through urine. Tubular damage causes reduced ability of absorption and secretion of uric acid and causes an increase in uric acid levels in the blood.[24,25]

Creatinine comes from a substance called creatine, which is formed when food turns into energy through a metabolic process. About 2% of body creatine is converted to creatinine every day. Creatinine is transported through the bloodstream to the kidneys. The kidneys filter out most of the creatinine and throw it in the urine. Therefore if the kidney is disrupted, creatinine in the blood serum increases. High creatinine levels indicate kidney damage or failure, even before patients complaints arise.[21] It is consistent with the study of Suryawan *et al*., where serum creatinine levels are directly proportional to the degree of glomerular damage.[23] Creatinine is released from the blood by the kidneys. Damage to the glomerular causes reduced glomerular filtration which causes blood creatinine levels to increase. The wider the glomerular damage, the less creatinine is filtered out. The level of glomerular damage affects creatinine levels in the blood so that creatinine levels in the blood and urine can be used to calculate creatinine clearance, as well as GFR.[21-23] Low creatinine levels in the blood, are used as important indicators of kidney function and can be used to determine whether a person with impaired renal function needs hemodialysis or not.[23,26-28]

Research by Okamura *et al*. states that in rats with extensive kidney damage with galectin-3 deficiency, total collagen increased, but myofibroblast (Mfb) synthesis and extracellular matrix decreased.[28] These results are in accordance with the study of O'Seaghdha *et al*. that found that in high serum galectin-3 levels there was a decrease in GFR in the incidence of CRF.[29] Tan *et al.* stated that galectin-3 levels in CRF patients with hemodialysis (GFR < 15 mL/min) higher than the control group.[30] It showed that galectin-3 affects the kidneys from chronic injury and fibrosis.

The test results of the relationship between galectin-3 levels and creatinine acid levels were obtained by r = 0.381 with p = 0.029, meaning there was a weak positive relationship. Rebholz stated that galectin-3 was related to urine albumin-creatinine ratio (UACR), r = 0.08, P <0.001.[31] The result was in accordance with Song *et al*. that was p <0.001.[32]

Uric acid is mainly synthesized in the liver which is catalyzed by the xanthine oxidase enzyme. Uric acid is transported to the kidneys by blood to be filtered, partially reabsorbed, and finally excreted through urine. Increased uric acid levels in urine and serum (hyperuricemia) depend on kidney function, the speed of purine metabolism, and dietary intake of foods containing purines. Purines derived from nucleic acid catabolism in the diet are converted into gout directly. The breakdown of purine nucleotides occurs in all cells, but uric acid is only produced by tissues containing xanthine oxidase especially in the liver and small intestine.[11]

Xanthine will be converted by xanthine oxidase to uric acid. Uric acid in the kidneys will experience four stages, namely uric acid from the capillary plasma into the glomerulus and filtration in the glomerulus. Around 98-100% will be reabsorbed in the proximal tubule, then secreted into the distal lumen of the proximal tubule and reabsorbed in the distal tubule.

Uric acid will be excreted in the urine around 6% - 12% of the amount of filtration. After vein filtration in the glomerulus, almost all reabsorbed in the proximal tubule.[12,16,30]

Mazzali *et al.* state that gout can be associated with worsening renal function, increased proteinuria, glomerulosclerosis, renal interstitial fibrosis, and preglomerular vasculopathy.[33] High uric acid can stimulate aldosterone secretion, an adrenal gland hormone that functions to increase blood pressure. High blood pressure causes the kidneys to work extra so that they can cause inflammation. Inflammation can increase galectin-3 which will trigger fibrogenesis.

The role of galectin-3 in renal fibrosis is still investigated, but galectin-3 deficiency causes a decrease consistent with MFb activation.[34] Galectin-3 deficiency inhibits MFb accumulation/activation and fibrosis, while thinning of specific macrophages reduces fibrosis severity where galectin-3 deficiency does not affect macrophage recruitment or proinflammatory cytokine profile of macrophages in response to interferon-γ/lipopolysaccharide.[33] Galectin-3 secretion by macrophages is very essential in activating renal fibroblasts to the profibrotic phenotype so that galectin-3 deficiency causes a decrease consistent with MFb activation.[34]

Galectin-3 deficiency increases total collagen, but there is a decrease in myofibroblast synthesis and extracellular matrix.[35] Galectin-3 could protect renal tubules from chronic injury by limiting apoptosis and improving matrix and fibrosis remodeling. Serum uric acid levels cannot predict the incidence of CRF but are independently associated with the progression of CRF that has already occurred.[16,36] CRF is associated with increased vascular risk. A study by Mok *et al*. in 2012, stated that serum uric acid levels were associated with serum creatinine levels and inversely related to GFR.[37]

The test results of the relationship between galectin-3 levels and serum uric acid levels were obtained by r = 0.347 and p = 0.048, meaning there was a weak positive relationship. This result was following Opotowsky's research; Galectin-3 increases with increasing uric acid with r = 0.36; p = 0.003.[38]

The research limitations were the sample size is relatively small and can affect the strength of the study to detect the results of studies that show a weak positive relationship. Thus, the correlation of galectin-3 with uric acid and creatinine, requires further research, not only to validate the robustness of our findings but also to show that galectin-3 can provide information as an alternative biomarker and other clinical variables.

CONCLUSIONS AND SUGGESTIONS

Based on the results of research in CRF patients with hemodialysis it can be concluded that: There is a significant weak positive relationship between galectin-3 levels and serum creatinine levels as a marker of kidney function; There is a significant weak positive relationship between galectin-3 levels and serum uric acid levels as a marker of kidney function.

Based on the results of the study and the limitations of the study, it is recommended: Further assessment of galectin-3 levels, creatinine levels, and serum uric acid levels are needed as an additional parameter to assess kidney function; Grouping patients with CRF without hemodialysis needs to be considered in further research.

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